Exogenous Estrogen and Breast Cancer After Bilateral Oophorectomy

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Estrogen use in 119 women in whom breast cancer developed after surgically induced menopause was compared to use among an equal number of controls matched for age, date of bilateral oophorectomy, and duration of follow-up. No increased risk for estrogen use *versus* no use was evident (relative risk = 0.7). When the authors examined three measures of estrogen dose—number of chart notations of estrogen use, time since first use, and duration between first and last use—only those with ≥5 notations had any significantly elevated risk (relative risk = 2.1; confidence limits 1.2–3.6), and there was a significant trend toward increasing risk with more notations ($P = 0.03$). Use specifically of conjugated estrogens was also associated with an increasing risk with more notation of estrogen use ($P = 0.07$). However, the other two measures of dose did not confirm this trend. Matched multiple logistic analysis suggested that number of notations of estrogen use conferred increased breast cancer risk (relative risk = 1.7), in dose–response relationships, but this result could have occurred by chance. Because of a lack of consistency, the generally low and statistically nonsignificant relative risks, and the lack of consistent effect modification in high-risk groups, the authors were unable to demonstrate a clear increased risk of breast cancer associated with replacement estrogen use.

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BREAST CANCER is more common in women with early menarche, late menopause, and nulliparity, whereas premature surgical menopause and early age at first pregnancy are associated with reduced breast cancer risk.[1] For a neoplasm with risk factors so clearly related to endogenous estrogens, the possible deleterious influence of exogenous estrogen use has been a reasonable concern. In investigations to date, oral contraceptives have not been implicated as etiologic factors, but postmenopausal replacement estrogens, which had seemed safe on the basis of early studies,[2–9] have become suspect as a result of one follow-up[10] and four case–control studies.[11–14] The magnitude and statistical significance of the relative risks of breast cancer according to estrogen use and presence or absence of ovaries have been inconsistent in these studies and more evaluation is clearly needed.

We report here a case–control study of estrogen use and breast cancer in a group of women who had oophorectomy. Our interest in this group was stimulated by the reduced risk of breast cancer in oophorectomized women,[15] and by our expectation that they would begin taking estrogens earlier in life and use them for a longer period than women who undergo natural menopause. Our study subjects were drawn from a large prepaid health plan; long-term follow-up was available from stored medical records.

Methods

Lists of operations performed in all Northern California Kaiser Foundation Health Plan hospitals were reviewed, and all those coded as bilateral oophorectomy (from the International Classification of Diseases 8th ed., Adapted [ICDA],[15a] 67.4) or removal of a remaining ovary (ICDA, ed. 8, 67.5) were transcribed to create a file of 18,820 women who had these procedures from 1953 through 1979. Substantial numbers of operations were not recorded until 1959. From a computer-stored file of hospital discharges from 1971 through 1979, supplemented by manually transcribed hospital discharges from 1960

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TABLE 1. Cases and Controls Having Conditions Present Within a Month Before Oophorectomy

Condition	ICDA	Cases	Controls
Genital Neoplasia			
Malignant	182, 183, 234	12	8
Benign			
Fibromas	218	95	87
Other	219–221	38	41
Ovarian diseases, *e.g.*, cysts	615	37	45
Infection	613, 614, 616, 620	59	61
Other cervical diseases	621	8	10
Uterovaginal prolapse	623	2	5
Other uterine diseases, *e.g.*, endometriosis	625	49	47
Menstruation disorders	626	34	25

ICDA: International Classification of Diseases 8th ed., Adapted.[15a]

through 1971, 3537 women with breast cancer were identified. We cross-matched these two files to identify women who were first diagnosed as having breast cancer after both ovaries had been removed. We required that the oophorectomy was performed before the women reached age 55.

An experienced medical record analyst reviewed the charts of potential cases to confirm the breast cancer diagnoses from pathology reports and to document that both ovaries were removed. A control subject was chosen from the file of women who had oophorectomies to match each case for year of birth and year of oophorectomy, and for date of entry into health plan membership within 1 year. The analyst then masked all entries in the medical records after a reference date 6 months before the diagnosis of breast cancer and after the same date for each case's control. A second record analyst, unaware of the hypothesis being studied or the case or control status of the subject, reviewed these records, transcribing detailed information on estrogen use, breast cancer risk factors, and associated medical conditions onto a standardized precoded form.

The list of estrogen substances sought included all those marketed during the period of the study. We recorded the drug used, the medical instruction given, *e.g.*, refill, discontinue, increase dosage, the route of administration, the dosage interval, and the number of refills, whenever available. In our analysis, we used three measures for quantifying estrogen use: (1) the time between the first notation of estrogen use and the reference date, which we called latency; (2) the interval between the first and last notation of estrogen use, which we called duration; and (3) the total number of chart notations of estrogen use. Because 98% of women who used estrogen began within the first year after oophorectomy, the measure of latency is similar to the time between oophorectomy and the reference date. Although the data did not allow for more precise measures of dose, in past studies, the number of notations of estrogen use has correlated well with more refined measures such as total cumulative dose.[13]

Individual risk factors were evaluated by calculating relative risk estimates and 95% confidence intervals based on McNemar's chi square for matched pairs. When matching was dropped, confounding was controlled by stratification, and odds ratios were estimated by the Mantel-Haenszel procedure.[16] Linear trends were tested by the Mantel extension of that procedure.[17] Multiple logistic analysis for matched pairs was used for the simultaneous consideration of estrogen use and established breast cancer risk factors.[18] All significance probabilities (P) are for a one-sided test.

Results

There were 119 cases and controls that fit our criteria. As expected, cases and controls were similar with respect to year of birth and age at oophorectomy (mean and standard deviation [SD] of 1923 ± 7 and 47 ± 5 years, respectively, for both). The interval between oophorectomy and breast cancer varied from 6 months to 14 years

TABLE 2. Relative Risk of Breast Cancer Associated with Previously Established Risk Factors: Matched Pairs Analysis

Risk factor	No. of case-control pairs according to presence of risk factor*				Relative risk estimate	95% CI
	Both	Case only	Control only	Neither		
White race	67	26	15	3	1.7	0.9, 3.2
Age at menarche <13	10	16	12	13	1.3	0.6, 2.8
No full-term pregnancies	1	22	14	81	1.6	0.8, 3.1
Age at first birth ≥25	14	14	10	11	1.4	0.6, 3.1
Other breast disease	17	31	21	50	1.5	0.8, 2.6
Breast cancer in mother or sister	1	6	1	84	6.0	0.9, 38.5
College education	11	9	6	10	1.5	0.5, 4.2
Quetelet index >3.5 ($100 \times lb/in^2$)	27	19	26	24	0.7	0.4, 1.3

* Total number of pairs may be less than 119 because of missing values.

CI: confidence intervals.

TABLE 3. Relative Risk of Breast Cancer According to Several Measures of Estrogen Use After Oophorectomy: Matched Pairs Analysis

Any estrogen use	No. of case–control pairs according to presence of stated estrogen use				Relative risk estimate	95% CI
	Both	Cases only	Controls only	Neither		
Ever used	94	9	13	3	0.7	0.3, 1.6
Chart notations ≥5	25	37	18	39	2.1	1.2, 3.6
Yr since first used ≥3	65	10	12	32	0.8	0.4, 1.9
Yr used ≥3	31	24	13	51	1.8	0.9, 3.6

CI: confidence intervals.

(mean, 5.0; median, 4.2; SD, 3.3 years). Women with breast cancer had undergone oophorectomy for much the same reasons as their controls; the distribution of medical conditions recorded within 1 month before the operation was not substantially different (Table 1). The predominance of malignant genital neoplasms among the cases was attributable to six *in situ* cervical carcinomas *versus* only one among the controls.

We first examined established breast cancer risk factors in this study group (Table 2). With the possible exception of the Quetelet index of obesity, all relative risk estimates were of the expected magnitude and direction, although none reached statistical significance.

As expected, most of these women had used some form of estrogen replacement; only 16 cases (13%) and 12 controls (10%) had never used any estrogen. The use of any estrogen, regardless of type of route of administration, was associated with a reduced relative risk of 0.7 (Table 3), although this apparent protective effect for users could have occurred by chance. We sought evidence of a dose–response effect with our three proxy measures of quantity of estrogen use. No increased risk was seen for women whose first use of estrogen was more than 2 years prior to breast cancer compared with 2 years or less, but five or more notations of estrogen use was associated with a significantly increased relative risk estimate (relative risk = 2.1) compared with four or fewer notations. Duration of use for more than 2 years also was a source of increased risk (relative risk = 1.8), although this difference was not quite statistically significant.

We then examined specific types of estrogen and routes of administration. The four most common types were conjugated estrogens (used by 63% of women), diethylstilbestrol (by 11%), ethinyl estradiol (by 31%), and estradiol (by 6%). Estradiol was usually administered parenterally, whereas the others were almost all taken orally. When users of one type of estrogen were compared with nonusers of that type, risk was increased for all types except ethinyl estradiol. Only diethylstilbestrol users were at greater risk that was statistically significant (relative risk = 2.5) (Table 4). When route was considered, users of injectable estrogen were at increased risk but not to a statistically significant degree.

We ignored the case–control matching to examine the data for possible dose–response trends. Age at oophorectomy and interval between oophorectomy and reference date, which had been controlled by matching, were used to stratify the data in this analysis. We found a U-shaped relationship having a statistically significant linear trend for the number of chart notations (Table 5). However, no particular trend was noted for latency or duration.

Conjugated estrogens were the most commonly used type of estrogen in our subjects and have been the focus of most previous studies of exogenous estrogen use and

TABLE 4. Relative Risk of Breast Cancer by Type of Estrogen Use and Route of Estrogen Administration: Matched Pairs Analysis

Type/Route	No. of case–control pairs according to estrogen use of stated type or route				Relative risk estimate	95% CI
	Both	Case only	Control only	Neither		
Type of estrogen						
Conjugated	46	30	28	15	1.1	0.6, 1.8
Diethylstilbestrol	2	15	6	96	2.5	1.0, 6.2
Ethinyl Estradiol	14	18	27	60	0.7	0.4, 1.2
Estradiol	1	8	4	106	2.0	0.6, 6.5
Route of administration						
Oral	92	10	14	3	0.7	0.3, 1.6
Injection	2	10	7	100	1.4	0.5, 3.7
Other	1	10	9	99	1.1	0.5, 2.7

CI: confidence intervals.

TABLE 5. Relative Risk of Breast Cancer by Certain Measures of Any Estrogen Use After Oophorectomy: Unmatched Analysis Controlling for Age at Oophorectomy and Interval Between Oophorectomy and Reference Date

Level any estrogen	Cases	Controls	Odds ratio*	Significance (trend)
Chart notations				
None	16	12	1.0	
1–4	41	64	0.5	$P = 0.03$
5–9	38	29	1.1	
10+	24	14	1.3	
Yr since first mentioned				
None	16	12	1.0	
<3	28	30	0.7	$P = 0.79$
3–5	32	31	0.8	
5+	43	46	0.5	
Interval between first and last mentioned				
None	16	12	1.0	
<3	48	63	0.5	$P = 0.37$
3–5	26	13	1.7	
5+	29	31	0.5	

* Odds ratios are based on Mantel-Haenszel procedure with stratification for age at oophorectomy and interval between oophorectomy and reference date.

breast cancer. There was no evidence from our matched pair analysis of increased risk of breast cancer in women who had ever used conjugated estrogens (relative risk = 1.1) (Table 4). To examine dose–response trends for conjugated estrogen use, we again ignored the matching and controlled by stratification for age at oophorectomy and interval since oophorectomy (Table 6). As with estrogen use, regardless of type, the odds ratios increased with number of notations and reached 2.8 for over five notations. Again, however, there was no increasing trend with duration or latency and none with increases of milligram dose.

TABLE 6. Relative Risk of Breast Cancer by Conjugated Estrogen Use: Unmatched Analysis Controlling for Age at Oophorectomy and Interval Between Oophorectomy and Reference Date

Conjugated estrogens	Cases	Controls	Odds ratio*	Significance (trend)
Chart notations				
None	43	45	1.0	
1–4	39	49	0.8	$P = 0.07$
5–9	26	20	1.4	
10+	11	5	2.8	
Years since first used				
None	43	45	1.0	
<3	26	22	1.3	$P = 0.56$
3–5	22	22	1.1	
5+	28	30	0.9	
Yr used				
None	43	45	1.0	
<3	44	47	1.0	$P = 0.41$
3–5	15	7	2.2	
5+	17	20	0.8	
Dose used longest				
None	43	45	1.0	
0.625 mg	14	11	1.3	$P = 0.42$
1.25 mg	53	47	1.2	
2.50 mg	4	6	0.6	

* Odds ratios are based on Mantel-Haenszel procedure with stratification for age at oophorectomy and interval between oophorectomy and reference date.

The effects of six breast cancer risk factors and two measures of estrogen use were evaluated simultaneously in a multiple logistic analysis for matched pairs (Table 7). Risks for over five notations of estrogen and for use of more than 3 years' duration remained elevated, but were weakened and not significant.

In other analyses, we restricted the study group to women who had at least 3 years between oophorectomy and the reference date, thus excluding women whose estrogen use was so close to the diagnosis of breast cancer that an etiologic role for estrogen seemed unlikely. This restriction did not alter our results substantially. Stratification by the Quetelet index of obesity produced no significant relationships by any measure of estrogen use. Also, in looking for modification of the effect of estrogens within high-risk subgroups, we stratified by age of menarche greater or less than 13 years, presence or absence of benign breast disease, and age at first full-term pregnancy greater or less than 25 years of age. We found no subgroups in which the risk of estrogen use was consistently enhanced.

Discussion

This matched case–control study was limited by design to women at reduced risk of breast cancer because of a prior bilateral oophorectomy. Exogenous estrogens were used at some time, usually soon after the operation, by 88% of our subjects. In general, if an exposure is ubiquitous among those at risk, it is difficult to identify an increased risk from that exposure. Because of the small size of the group who never used estrogen, our study lacked statistical power for the comparison between that group and women who had ever used estrogen. We were more likely to see an effect of estrogen, if present, by looking for a high-dose effect or a dose–response trend or by studying conjugated estrogens only. For example, in our comparison of women with or without five or more notations of any estrogen, for which there were 55 discordant pairs, our statistical power to detect an odds ratio of 2.0 was 0.81 for a one-sided McNemar test.[19] We found that those women who had the most chart notations of any estrogen or of conjugated estrogens had higher risks of breast cancer and that this relationship was statistically significant. However, this high-dose effect is difficult to translate into a practical expression of cumulative dose, and can be viewed as suggestive only.

A high-dose effect was not seen with our measures of duration of use or latency for all estrogens or conjugated

estrogens and not for the milligram dose of conjugated estrogens usually taken. One possible reason why duration and latency effects were not found may be related to the relatively modest duration of follow-up. Although it ranged up to 14 years, the mean was only 5.0 years. If the putative effect of exogenous estrogen on breast cancer was long-term, *e.g.*, 20 to 30 years, it would not have been seen in this study. Long-term effects may not be important in women who have natural menopause because the potential expression of an increased risk, *i.e.*, breast cancer, would only occur at the end of the usual life span. However, women who have early surgical menopause may still be subject to such possible long-term risks.

Our results can be compared with recent studies in which evidence of an increased risk associated with estrogen was more convincing (Table 8). Relative risk estimates have ranged from 1.1 to 1.3 for all women taking estrogens,[10–13] and have been significantly elevated in two of these studies.[12,13] Among women having oophorectomy, relative risks associated with estrogen use have ranged from 0.8 to as high as 1.5, although none have been statistically significant. From Table 8, we can see that these recent studies have been inconsistent with respect to which ovarian status is at highest risk from estrogen use and whether or not dose effects and risk modification have been present.

Our study had several aspects which acted to minimize any bias in ascertainment or misclassification of exposure. Both the breast cancer outcome and the presence of bilateral oophorectomy were well documented. A standardized format was used to abstract information already recorded in the medical record, and the person abstracting the information on estrogen use was blind to both the hypothesis and the case or control status of the subject. Thus, ascertainment bias was unlikely for information that was recorded in the medical records. Total number of notations, which was the measure of cumulative estrogen dose with the strongest relationship to breast cancer in our study, is probably an underestimation of the true number of times an instruction to use estrogen was given to a patient. However, any underestimation should have been of the same magnitude in both cases and controls and would be unlikely to affect our risk estimates. On the other hand, the number of notations could have been influenced by the number of physician visits and may not reflect higher actual estrogen use; that is, the number of notations might reflect personal characteristics related to more frequent visits to physicians than actual estrogen dosage.

We believe that these results do not support a strong role for postmenopausal estrogen use in breast cancer at

TABLE 7. Multivariate Adjusted Relative Risk of Breast Cancer From Matched Logistic Analysis

Variable	Odds ratio	*P* values	95% CI
White race	1.9	0.03	0.9, 3.8
Age at menarche <13	1.7	0.07	0.8, 3.4
Age at first birth ≥25	1.3	0.25	0.6, 2.7
Other breast disease	1.4	0.15	0.8, 2.6
College education	1.2	0.37	0.5, 2.7
Quetelet index <3.5*	0.8	0.25	0.4, 1.5
All estrogens ≥5 chart notations	1.7	0.07	0.8, 3.5
All estrogens ≥3 yr of use	1.3	0.25	0.6, 3.1

* $100 \times lb/in^2$.
CI: confidence intervals.

TABLE 8. Results of Recent Studies Showing an Increased Risk of Breast Cancer With Replacement Estrogen Use

Study	Design	Cases	Non-cases	Relative risk estimate			Risk increased with:				
				All	Natural menopause	Oopho-rectomy	Increasing dose	Increasing duration	Benign breast disease	Lower parity	Positive family history
Hoover *et al.*, 1976[10]	Retrospective cohort	49	1842	1.3*	1.1	1.3	yes	yes*	yes	yes	—
Ross *et al.*, 1980[11]	Matched case–control	138	281	1.1	1.4	0.8	yes*†		yes	—	—
Brinton *et al.*, 1980[12]	Matched case–control	881	863	1.2*	1.2	1.5	yes	yes	yes	yes	yes
Jick *et al.*, 1980[14]	Case–control	157	157	—	3.4*	1.1	no	no	yes	—	—
Hoover *et al.*, 1981[13]	Case–control	345	611	1.3*	1.3	1.5	yes*	yes*	no	no	yes‡
Hiatt *et al.* (present study)	Matched case–control	119	119	—	—	0.7 1.1§	yes	no	no	no	—

* Statistically significant ($P < 0.05$).
† For total milligram accumulated dose.
‡ For heavier estrogen users.
§ For conjugated estrogens.

least for the durations of use present in our study group, *e.g.*, mean of 5 years. Taken with the results of the other well-designed studies having sufficient follow-up periods, it appears that if a real increase in breast cancer risk does exist in estrogen users, it is much smaller than that for endometrial cancer and only of possible concern at higher doses and durations. It is heartening to observe that even if further studies more clearly implicate replacement estrogens as a breast cancer risk factor, women will already have begun to benefit from changes in current medical practice toward use of less and of lower-dose estrogen following the earlier epidemiologic studies of estrogens and endometrial cancer.

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